EXHIBIT 12

EXPERT REPORT

Depakote Claims
v.
Abbott and AbbVie

By: Linda A. Motyka, Ph.D.
MedTrek®, Inc.

September 26, 2017

1. INTRODUCTION

DOCUMENTS REVIEWED

The documents reviewed for this report are found in Exhibit 1 and also referenced within the report. If additional information becomes available, rights are reserved to supplement this report.

COMPENSATION

For this matter, compensation is at a rate of $ 450./hour (per report). For deposition and trial testimony, compensation is at a rate of $ 650./hour.

PREVIOUS DEPOSITIONS AND TESTIMONY – PAST 5 YEARS

Silverman v. Watson Laboratories, Inc. Florida and Watson Pharma, Inc and Capsugel, Inc.

Depostition: December 6, 2012
Philadelphia, PA
U.S.D.C. – Southern District of Texas, Houston Division
No. 4:10-cv-1952

Guddeck, et al. v. SmithKline Beecham Corporation d/b/a GlaxoSmithKline *[Paxil Claims]*

Deposition: September 4, 2014
Philadelphia, PA
U.S.D.C. – Minnesota
No. 13-cv-2508 (MJD/LIB)

Kiker v. SmithKline Beecham Corporation d/b/a GlaxoSmithKline *[Paxil Claims]*

Deposition: February 24, 2016
Philadelphia, PA
U.S.D.C. - Southern District of Ohio
No. 2:14-cv-02164-EAS-TPK

BRIEF SUMMARY OF QUALIFICATIONS

My CV is provided in Exhibit 2. I have more than 25 years of experience in the pharmaceutical industry including the areas of regulatory affairs, quality control and quality assurance, drug development, chemistry and manufacturing and compliance with FDA regulations. I have a Ph.D. in organic chemistry and I have experience in writing and implementing Standard Operating Procedures for the pharmaceutical industry and experience in labeling of pharmaceutical drugs.

The opinions being addressed in this report are within a reasonable degree of scientific certainty based upon the documents reviewed and my knowledge of science, drug development, regulations (including FDA regulations/regulatory affairs) and quality control and quality assurance for the pharmaceutical industry.

The law firm of Heninger Garrison Davis LLC requested my opinion regarding birth defect cases, including regulatory opinions on valproic acid/divalproex sodium (VPA, Depakene and Depakote and Depacon) and birth defects and the labeling of the products.

2. BACKGROUND

2.1 Active Pharmaceutical Ingredient (API)

The API is often referred to as VPA (valproic acid and/or divalproex sodium and/or valproate sodium) throughout this report.

2.1.1 Depakene (valproic acid)

Depakene (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. Valproic acid occurs as a colorless liquid with a characteristic odor. Valproic acid has the following structure:

$(CH_3CH_2CH_2)_2 — CH — COOH$

2.1.2 Depakote (divalproex sodium)

Divalproex sodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Chemically it is designated as sodium hydrogen bis(2-propylpentanoate). Divalproex sodium occurs as a white powder with a characteristic odor. Divalproex sodium has the following structure:

$[(CH_3CH_2CH_2)_2 — CH — COOH \bullet (CH_3CH_2CH_2)_2 — CH — COONa]$, [1:1]

2.1.3 Depacon (valproate sodium)

Valproate sodium is the sodium salt of valproic acid. It is a white and odorless, crystalline powder and has the following structure:

$(CH_3CH_2CH_2)_2 — CH — COONa$

2.2 Abbott Regulatory Submissions

2.2.1 Depakene

IND 11,152, submitted to FDA 13 DEC 1974
NDA 18081, capsules, approved 28 FEB 1978
NDA 18082, syrup, approved 28 FEB 1978

Depakene is currently approved for the following indications:

- Monotherapy and adjunctive therapy of complex partial seizures
- Sole and adjunctive therapy of simple and complex absence seizures
- Adjunctive therapy in patients with multiple seizure types that include absence seizures

Valproic acid (VPA) had been on the market in France since the 1960's. Abbott submitted NDAs (NDA 18081 and 18082) to the FDA for Depakene marketing approval in 1977 for epilepsy indications. Most of the clinical studies data for valproic acid at that time were from outside the US.

2.2.2 Depakote

Depakote (Delayed Release)
IND 18,872, submitted to FDA 29 DEC 1981
NDA 18723, tablet – delayed release, approved 10 MAR 1983, epilepsy indications

- NDA 20-320: Approved 26 MAY 1995 for mania (bipolar)
- Supplement S-017, approved 18 MAR 1996 for "prophylaxis of migraine headaches"

NDA 019680, capsule – delayed release pellets

Depakote CP
NDA 019794, tablet – delayed release, approved 11 JUL 1990 (discontinued)

Depakote ER (Extended Release)
NDA 021168, approved 4 AUG 2000, migraine prophylaxis

- Supplement S-012, approved 6 DEC 2005, acute manic or mixed episodes associated with bipolar I disorder, with or without psychotic features

NDA 020782, new dosage form, approved 20 DEC 2002, epilepsy indications
NDA 022267, approved 24 MAR 2008, children & adolescents

Depakote is currently approved for the following indications:

- Treatment of manic episodes associated with bipolar disorder

- Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures
- Prophylaxis of migraine headaches

2.2.3 Depacon

NDA 020593, intravenous injection, approved 30 DEC 1996

Depacon is currently approved for the following indications:

- Monotherapy and adjunctive therapy of complex partial seizures and simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures

2.3 Specifics of Cases

2.3.1 Burnett/McCall

Danial Burnett was born on [redacted] in South Carolina and diagnosed with spina bifida. His mother, Irena McCall, had taken Depakote during her pregnancy for a seizure disorder. There is no indication that Irena McCall was practicing any method of birth control prior to becoming pregnant.

The Depakote labeling Patient Information Leaflet from the JAN 1998 Abbott labeling and contained in the 1999 PDR (Physician's Desk Reference) is discussed in 3.5. Abbott structured the Depakote Patient Information Leaflet only for women who could become pregnant for migraines and no other indications. Irena McCall would not have received important information relating to spina bifida since she was taking Depakote for epilepsy.

2.3.2 Anderson/Sansone

A.S. was born on [redacted] in Missouri with a head deformity – hypercentosis of the skull and other malformations. His mother, Marthee Sansone, had taken Depakote during her pregnancy for seizure disorders. Marthee Sansone was planning to become pregnant and, therefore, not practicing any method of birth control.

3. ANALYSIS AND OPINIONS

3.1 Risk of Spina Bifida

Abbott has represented the risk of spina bifida as 1-2% in the labeling of VPA from 1983 to present (2017). The risk of spina bifida was based on the data from Lyon

France (1982-1983). Abbott has represented and misrepresented this data throughout the approximate 35 years of marketing of VPA in its labeling (package insert and leaflets)

3.1.1 FDA Advisory Committee Meeting of 12 OCT 1977 [REF 2]

The FDA Neurologic Drugs Advisory Committee met on 12 OCT 1977 to address issues relating to the approval for marketing of Depakene in the US for epilepsy indications *(Meeting Minutes, FOI Services #6911A)*. Abbott presented the following results of their teratogenicity studies in animals and rat reproduction and fertility studies to the Committee. The following in italics is from the Advisory Committee Meeting Minutes, including the end statement.

Teratogenicity Study

Organism	*Reactions*	*Dose (mg/kg)*
Mouse	*no toxicity*	*65*
	skeletal abnormalities	*150 and 350*
Rat	*no toxicity*	*65*
	skeletal abnormalities	*150 and 350*
Rabbit	*no toxicity*	*150*
	skeletal abnormalities	*350*

Rat Reproduction and Fertility Studies

Reactions	*Dose (mg/kg)*
no effect	*65 and 150*
Fewer highest dosed females were pregnant	*350*
Reduction in litter size at	*350*
Nearly 100% mortality when nursed by their dame *40% survival when offspring shifted to control dame.*	*350*

At this point due to same inquiry from the Committee concerning what was judged to be a significant toxic effect, Abbott explained they felt toxicity to be significant when statistically significant differences occur between dosage group and control.

The Committee also unanimously recommended to the FDA that Abbott carry out continued safety studies on the embryogenesis of valproic acid. The meeting minutes read:

> *"After the discussion from each Committee member as to his opinion of the data in support of Abbott's NDAs for valproic acid, the Committee moved unanimously to recommend to the FDA approval for marketing of Depakene for absence seizures alone or in combination at doses up to 30 mg/kg/day. The Committee also unanimously moved that it recommend to the FDA and Abbott to carry out continued studies on safety with regard to hepatic side effects, embryogenesis carcinogenesis, and also to encourage study to determine the efficacy of sodium valproate in the treatment of myoclonic seizures, febrile seizures and infantile spasms."*

The FDA Neurologic Drugs Advisory Committee concluded from Abbott's presentation of data at the meeting of 12 OCT 1977 that Depakene (VPA) was significantly toxic and continued safety studies needed to be done by Abbott with regard to embryogenesis. During the very early development of VPA by Abbott, embryogenesis was identified as a very important issue.

3.1.2 FDA and CDC and Abbott Interactions [REF 3]

Memo of Telephone Conversation: G. Oakley (CDC) and A. Ruskin (FDA): 13 SEP 1982 – FOI Services #79287A

Abbott had submitted its NDA (NDA 18723) for Depakote (divalproex sodium, same active ingredient as in Depakene) to the FDA for epilepsy indications in DEC 1981. On 10 SEP 1982, Dr. Godfrey Oakley at the CDC (Center for Disease Control) in Atlanta alerted Dr. Jones at the FDA about "possible valproic acid – spina bifida link in Lyon, France". The memo continued with additional information. "At the International Clearinghouse of Birth Defects Monitoring Programs meeting in London, September 6-8, 1982, Professor Robert and his daughter, Elizabeth, geneticists at the Institution European Genomutations, 80 Rue Edmond Locard 69005, Lyon, reported 9 children born with overt, operated on, spina bifida whose mothers received valproic acid in the first trimester … In the last 2 years there were 50 babies with spina bifida. Of the nearly 20% whose mothers received valproic acid 7 of 9 received that drug only." At the bottom of the memo, Dr. Paul Leber, FDA, has a handwritten note:

a) Copies to all Valproate NDA/IND
b) Copy to review
9/16/82 c) Called J. Jones, did not reach her
left message about our interest
in her division's evaluation/plans to

[unknown] with them "signal" event

The memo also stated "Exencephaly or anencephaly are poorly monitored in their system and were absent". Only spina bifida was evaluated. Dr. Leber from the FDA considered this data a safety "signal".

Memo of Telephone Conversation: G. Oakley (CDC) and P. Leber (FDA): 29 OCT 1982 (FOI Services #79287A)

Dr. Leber wrote a memorandum of telephone conversation on 29 OCT 1982 of a conversation between him and Dr. Oakley with the subject "Discussions Between Dr. Oakley (CDC) and Abbott's Representatives on the Subject of Depakene's Teratogenicity". Dr. Oakley (CDC) phoned Dr. Leber (Director, FDA Neuropharmacological Drugs Division) to tell him about his meeting on 28 OCT 1982 with Abbott and its representatives. The meeting discussed the results of Dr. Robert from Lyon and spina bifida and valproic acid – Depakene's teratogenicity. Abbott took the position that they wanted to "independently visit France prior to making any further commitments about the validity of the findings". Abbott and the CDC "came to no agreement about an expanded registry." Abbott wanted "another two weeks and an exchange on position papers prior to making a decision on the registry." Additional studies were discussed including:

- A retrospective study of women exposed to Depakene in England – approximately 110 patients with 3-5 events (spina bifida or abortions)
- Another cohort of Depakene exposed with a higher rate of malformations (approximately 20%) – Abbott was being somewhat "cagey" in their description of this data base(s).

CDC MMWR (Joint CDC/FDA Report): Valproic Acid and Spina Bifida: A Preliminary Report – France, 29 OCT 1982 [REF 13]

On 29 OCT 1982, the CDC published an "International Note" in its "Mobidity and Mortality Weekly Report" entitled "Valproic Acid and Spina Bifida: A Preliminary Report – France." The article reported on the information that the CDC had available from Dr. Robert in Lyon France. The data showed a "highly statistically significant odds ratio of 20.6 – the odds ratio is an estimation of relative risk in case-control studies." Two 2 X 2 tables of data were presented (Table 1 is given below):

Table 1: Spina bifida (SB) and treatment with valproic acid (VA) of mothers who have delivered infants with birth defects – Lyon, France			
	SB	**Other birth defects**	**Total**
VA treatment	9	21	30
No VA treatment	137	6,595	6,732
Total	146	6,616	6,762
Odds ratio = 20.6; 95% confidence limits 8.2-47.9; p<0.000001 (2-tail)			

The Odds Ratio (OR) was calculated from the standard 2X2 table:
[(9/21) / (137/6595] = 20.6

The OR of 20.6 means that a pregnant woman taking valproic acid for epilepsy is 20.6 times more likely to have a baby with spina bifida than a pregnant woman not taking valproic acid. This data gives information only on spina bifida (no other neural tube defects).

Based on the relative risk/odds ratio (OR=20.6) as determined from the French data and the US spina bifida rate of approximately 6 per 10,000 births, the estimated risk of valproic acid-exposed women having children with spina bifida was determined to be 1.2%. The estimated risk of 1.2% is a calculated estimated risk based on the Bayes theorem:

[(6/10,000) X 20.6] = 0.0123 or (multiply by 100 for %) 1.2%. The 1.2% is NOT an incidence of spina bifida; it is a calculated estimated risk based on case control studies. The 1.2% means that in the general pregnant population, women have a 1.2% calculated estimated risk of having a baby with spina bifida if they take valproic acid.

The CDC noted "This risk is similar to that for women who have had previous children with neural-tube defects (anencephaly or spina bifida). The CDC also wrote "All anticonvulsants, including valproic acid, carry a warning of potential human teratogenicity in their labeling."

FDA Talk Paper: Valproic Acid and Spina Bifida: 5 NOV 1982 (FOI Services 79284A) [REF 1]

On 5 NOV 1982, the FDA summarized the findings of the Lyon France data in its own notice "FDA Talk Paper". The summary was consistent with the CDC MMWR weekly publication of 29 OCT 1982. Both had the following statement regarding congenital malformations:

The American Academy of Pediatrics Committee on Drugs offered the following recommendations on how to convey the risk to women: "When a woman who has epilepsy and requires medication asks about pregnancy, she should be advised that she has a 90% chance of having a normal child, but that the risk of congenital malformations and mental retardation is two to three times greater than average because of her disease or its treatment."

CDC MMWR Report, Valproate: A New Cause of Birth Defects – Report from Italy and Follow-Up from France, 26 AUG 1983 [REF 14]

The CDC updated its information relating to the Lyon France and this is shown below in Table 3, as depicted in the MMWR report.

Table 3: Association between spina bifida aperta (SB) and treatment with valproic acid (VA) of mothers who have delivered infants with birth defects – Lyon, France

	SB	Other birth defects	Total
VA treatment	10	21	30
No VA treatment	140	7,566	7,706
Total	150	7,587	7,737
Odds ratio = 25.7; 95% confidence limits 10.9-58.6; p<0.001			

With the updated data from Lyon France, a recalculation of the odds ratio increased it to 25.8. The CDC also reported on additional information of spina bifida in mothers taking valproic acid/valproate from Italy and the UK. A UK study showed that "… of infants born to 196 pregnant women treated with valproic acid, 157 (80%) were normal and nine (5%) had spina bifida. The remaining 30 infants had other structural defects, including cardiovascular defects, orofacial clefts, and digital abnormalities…"

With these new data, the CDC concluded "valproic acid and sodium valproate should be considered human teratogens. CDC has estimated that a pregnant woman in the United States treated with these drugs would have a 1%-2% risk of having a child with spina bifida." The 1%-2% determination is a calculated estimated risk for spina bifida is not an incidence.

Additionally, the CDC stated "Little is known about the relationship between valproic acid and other birth defects. To better define the risk of such therapy, the CDC is assembling a registry of women taking valproic acid during pregnancy". The CDC concluded that valproic acid/valproate caused birth defects and was a human teratogen.

FDA Reviewer Guidance: Evaluating Risks of Drug Exposure in Human Pregnancies, APR 2005 [REF 11]

The FDA published this guidance for its Clinical/Medical reviewers *(https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071645.pdf)*. The guidance discusses the different types of sources of human data on gestational drug exposures (shown below), including how they relate to VPA teratogenicity:

Sources of Human Data on Gestational Exposures

A. Case Reports
B. Epidemiology Studies
1. Prospective Studies
a. Cohort studies
b. Pregnancy exposure registries
2. Retrospective Studies
a. Birth defect registries
b. Case control studies

Each source of human data is discussed within the FDA reviewer guidance. When the CDC stated in its MMWR "Valproate: A new Cause of Birth Defects – Report from Italy and Follow-up from France" that they were planning to establish a registry for VPA, the CDC was most likely referring to a birth defects registry (a retrospective study); it is not know at this time if the CDC ever set up this registry. The guidance discusses the Lyon France data for valproic acid under the "case control studies" (retrospective studies) section:

> "Although pregnancy exposure registries are limited to screening for major teratogens on the level of thalidomide or isotretinoin, case control studies have the statistical power to identify teratogens with more modest risks on the level of valproic acid. The main strength of case control studies is their ability to evaluate the risk of rare events, and in the setting of birth defects, this strength means that such studies are highly efficient in identifying the risk of specific birth defects."

The Lyon France data identified VPA as a human teratogen in 1982/1983. A teratogen is "anything known to cause birth defects during development of an embryo or fetus". *(see FDA Drug Safety Communication of 30 JUN 2011 for teratogen definition).* [REF 28]

3.1.3 Representations and Misrepresentations of Lyon France/CDC data in VPA Labeling

The Lyon France data has been represented and misrepresented throughout the marketing of VPA by Abbott (1982 through present) in the Depakote (VPA) labeling. The misrepresentation of the Lyon France data in the "Patient Information Leaflet" is discussed in Section 3.5 of this report.

1984 PDR

"BASED UPON A SINGLE FRENCH REPORT, THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1.2%. THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA)."

- The Lyon France data was based on a case control study involving 146 (at the time) cases of spina bifida, not a single French report. The risk was determined by the CDC to be "similar to that for women who have had previous children with neural-tube defects (anencephaly or spina bifida)" [REF 13], not "similar to that for non-epileptic women who have had children with neural tube defects (anencephaly and spina bifida)". This is not true since later labeling (PDR 2008) states "THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG) ESTIMATES THE GENERAL POPULATION RISK FOR CONGENITAL NEURAL TUBE DEFECTS AS 0.14% TO 0.2%." Abbott misrepresented the spina bifida risk.

1986 PDR

"THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%. THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA)."

- Changed from 1.2% to 1 to 2% to reflect the CDC Follow-up Report. [REF 14].
- The second sentence remained unchanged.

1993 PDR

"THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%."

- The statement that misrepresented the risk of the Lyon France data for about 10 years was removed – "THIS RISK IS SIMILAR TO THAT FOR NONEPILEPTIC WOMEN WHO HAVE HAD CHILDREN WITH NEURAL TUBE DEFECTS (ANENCEPHALY AND SPINA BIFIDA)".

1997 PDR/ MAR 1996 rev

There are no changes to the representation of data on the Lyon France study. However, about this time, Abbott added two new indications – mania and prophylaxis of migraines.

- Abbott failed to specify in its labeling that the estimated risk for spina bifida that was determined from the Lyon France study was from patients who were taking valproic acid for epilepsy. By not making this distinction after including the additional indications in the labeling, the spina bifida risk can be interpreted as including any or all indications, which is misleading. Abbott does make this distinction in its "Patient Information Leaflet" when it states "… Although the incidence is unknown in migraine patients treated with Depakote, approximately 1 to 2% of children born to women with epilepsy taking Depakote in the first 12 weeks of pregnancy …"

2008 PDR/ Depakote ER/OCT 2006 rev

A separate section for "Neural Tube Defects" was added to the labeling.

"THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%. THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG) ESTIMATES THE GENERAL POPULATION RISK FOR CONGENITAL NEURAL TUBE DEFECTS AS 0.14% TO 0.2%."

- While the second sentence is probably correct, it gives the impression that the two numbers (1 to 2% and 0.14 to 0.2%) are comparable, when they are not – one is for spina bifida, the other is congenital neural tube defects. A similar, and more distinct, mixing of the information occurs in the "Patient Information Leaflet" with the

statement "…Depakote has been associated with birth defects, in particular, with spina bifida and other defects related to failure of the spinal canal to close normally. Although the incidence is unknown in migraine patients treated with Depakote, approximately 1 to 2% of children born to women with epilepsy taking Depakote in the first 12 weeks of pregnancy had these defects (based on data from the Centers of Disease Control, a U.S. agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%."

- By mixing numbers between spina bifida data and "spina bifida and neural tube defects" data, Abbott presents the Lyon France study data as showing about a 10 times greater risk for spina bifida for patients taking valproic acid than those not taking valproic acid when the actual estimated data shows about a 26 times greater risk (odds ratio).

<u>2009 PDR/ Depakote ER/ MAR 2008 rev</u>

- Information remains the same, but the capitalization is removed.

<u>AUG 2014 rev/ Depakote DR</u>

"… Based on published data from the CDC's National Birth Defects Prevention Network, the risk of spina bifida in the general population is about 0.06 to 0.07%. The risk of spina bifida following *in utero* valproate exposure has been estimated to be approximately 1 to 2%."

- After 30 years of representing and misrepresenting the Lyon France study data on the estimated risk of spina bifida in mothers taking valproic acid in its labeling, Abbott presents a reasonable comparison between the incidence of spina bifida in the general population (actually used to calculate the estimated risk in mothers who took valproic acid by the CDC) and the estimated risk based on the Lyon France study.
- The Lyon France study was for valproic acid, not valproate.
- Abbott fails to specify in its labeling over the years (except in the Patient Information Leaflet) that the estimated risk for spina bifida that was determined from the Lyon France study was from patients who were taking valproic acid for epilepsy.
- Abbott also fails to specify, throughout its labeling (except in the Patient Information Leaflet), that the Lyon France study data was from women who took valproic acid in their first trimester.

3.2 Pregnancy Category D

Since the PDR 1985 edition Abbott labeled Depakote (VPA) as a Pregnancy Category D. The FDA published the regulation for Pregnancy categories in 1979; *see 79 FR 72063, 4 DEC 2014*. The FDA labeling requirements for drugs is in 21 CFR 201.57: Specific requirements on content and format of labeling for human prescription drugs. This section has been amended many times from the initial marketing of VPA through present. Since 1979 through 2014, the regulations in this section have remained mostly constant [21 CFR 201.57 (f)(6)]. For Pregnancy Category D, the regulation states the following:

"*Pregnancy Category D*. If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling shall state: "Pregnancy Category D. See 'Warnings' section." Under the "Warnings" section, the labeling states: "*(Name of drug*) can cause fetal harm when administered to a pregnant woman. (*Describe the human data and any pertinent animal data.)*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."[*(21 CFR 201.57 (f)(6)(i)(d), 1 APR 2005 edition]*

Abbott did not put the following statement in the Warnings Section of their labeling of Depakote/Depakene/Depacon from years 1983 – 2012 as required by FDA regulation 21 CFR 201.57(f)(6). **"Depakote (*name of drug)* can cause fetal harm when administered to a pregnant woman."**

Abbott only began placing the required statement "If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus" near the end of its Warnings Section in the year of PDR 1996 (Rev May 1995). Abbott was clearly aware of the required labeling regulation for a Pregnancy Category D drug. The statement "Valproate can cause fetal harm when administered to a pregnant woman" appears initially in the JUL 2013 labeling for Depakote.

In 2014 (AUG 2014 labeling), Abbott designated Depakote a Pregnancy Category X and it contraindicated Depakote for pregnant patients treated for prophylaxis of migraine headaches.

During the time that Abbott had VPA designated as a Pregnancy Category D drug (1983 – 2014), it only had the required statement "Depakote *(name of drug)* can cause fetal harm when administered to t pregnant woman" in its labeling from 2013 to present.

With the designation of Pregnancy Category D, Abbott always had the responsibility and was required to present the risks of birth defects so that physicians and healthcare professionals (as well as patients) could assess the benefit/risk for taking VPA during pregnancy.

3.3 Comparison of Depakote Labeling in the 1994 PDR (48th Edition) and the 1999 PDR (53rd Edition): Before Migraine Indication and After Migraine Indication

A comparison between the labeling for Abbott's Depakote DR (delayed release) Tablets in the 1994 PDR and 1999 PDR was made. This was before the prophylaxis of migraine indication (1994) and after the prophylaxis of migraine indication (1999). This was also before the indication for mania (1994) and after the indication for mania (1999). The labeling in the 1999 PDR has a revised date of JAN 1998 and includes a "Patient Information Leaflet". The FDA approved the indication for mania (Depakote DR tablets) on 26 MAY 1995 (NDA 20-320) and the indication for prophylaxis of migraines on 18 MAR 1996 (NDA 18-723/Supplement 17). It is noted that the 1994 label for Depakote Tablets is combined with Depakote Sprinkle Capsules and for the 1999 label, the two formulations have separate labels and the Sprinkle Capsules is only indicated for epilepsy.

As stated in the above section, neither label for Depakote has the required warnings statement for a Pregnancy Category D drug – "Depakote *(name of drug)* can cause harm when administered to a pregnant woman."

In the 1999 labeling, Abbott added the "Teratogenicity" section in the Black Box Warning at the beginning of the labeling.

> VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA), ACCORDINGLY, THE USE OF DEPAKOTE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. THIS IS ESPECIALLY IMPORTANT WHEN THE TREATMENT OF A SPONTANEOUSLY REVERSIBLE CONDITION NOT ORDINARILY ASSOCIATED WITH PERMANENT INJURY OR RISK OF DEATH (E.G. MIGRAINE) IS CONTEMPLATED. SEE WARNINGS, INFORMATION FOR PATIENTS.
> <u>AN INFORMATION SHEET DESCRIBING THE TERATOGENIC POTENTIAL OF VALPROATE IS AVAILABLE FOR PATIENTS.</u>

Although Abbott's 1999 PDR labeling has the statement that "an information sheet describing the teratogenic potential of valproate is available for patients" in the black box warning, there is only a patient information leaflet (at the end of the

labeling) for patients taking Depakote for prophylaxis of migraines and no other indications.

Both the 1994 and 1999 labeling of Depakote contain the following in the Warnings – Use in Pregnancy Section;

> THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

These statements have always appeared in the VPA labeling from the 1993 PDR through to the 2007 PDR. There are no references to support these statements and they are untrue. Pharmaceutical companies have been obtaining "adequate data on drug teratogenicity in humans" through analysis of retrospective study data and prospective study data (pregnancy exposure registries) for many years. The statements actually read like an excuse for not setting up a pregnancy exposure registry for Depakote. Even if these statements were true for epileptic drugs, which they are not, it doesn't address the indications of mania or migraines. In 2001, in the New England Journal of Medicine, the Genetics and Teratology Unit at Massachusetts General Hospital published a paper entitled "The Teratology of Anticonvulsant Drugs" *(L. B. Holmes et al, N Engl J Med, Vol. 344, No. 15, April 12, 2001).* [REF 16].

Lewis B. Holmes MD was a main author of the NAAED Pregnancy Registry, someone Abbott knew quite well. The authors, L.B. Holmes et al, addressed the issue of whether abnormalities in infants are caused by the maternal epilepsy itself or by exposure to anticonvulsant drugs. The authors concluded from their study "A distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of anticonvulsant drugs during pregnancy, rather than with epilepsy itself." The epileptic condition was not more important than drug therapy in contributing to congenital anomalies as stated in the Depakote labeling. Even though the results of this study were published in 2001 and the study was conducted from 1986-1993, Abbott added the statements described above in their labeling in 1993 and continued to keep these statements in their labeling through to 2007. The study was published in 2001. The statements were untrue and basically an excuse for Abbott to not conduct its own studies and subsequently not having more data on birth defects caused by VPA (identify birth defects and incidence of major malformations). The FDA's Reviewer Guidance "Evaluating the Risks of Drug Exposure in Human Pregnancies" *(APR 2005)* actually addressed this article by L.B. Lewis et al when it said "For example, after years of speculation, it was only recently that a study suggested that the increased risk for embryopathy seen in the offspring of women with epilepsy is associated with gestational exposure to anticonvulsants

rather than with epilepsy itself (Holmes 2001)." The statements in the Abbott labeling were from "years of speculation", according to the FDA. Abbott did not review clinical literature in an effort to update its labeling.

The statement ""THEREFORE, ANTIEPILEPTIC DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES" was contained in the 1994 PDR labeling and not in the 1999 PDR labeling – although, the black box warning was added to the 1999 PDR labeling. The 1994 PDR labeling was specific to epilepsy (the only approved indication at the time) and the 1999 PDR labeling focused on prophylaxis of migraines and not epilepsy or mania.

The statement "ANIMAL STUDIES HAVE ALSO DEMONSTRATED VALPROATE INDUCED TERATOGENICITY" was changed to "Animal studies have demonstrated valproate-induced teratogenicity."

3.4 Birth Control

The labeling for VPA does not state that women of childbearing potential must be practicing effective birth control while taking VPA. However, during the clinical studies for VPA, particularly for the migraine indication of Depakote DR (studies conducted from about 1991 through about 1995), the inclusion/exclusion criteria either excluded women of childbearing potential (Study M91-556) or required effective birth control (M92-811).

During the FDA review of the clinical studies for Depakote for approval of its new indication prophylaxis of migraines, the FDA Medical Reviewer (David Collins MD) wrote the following:

> "The risks using Depakote during pregnancy must be considered when using this drug for the treatment of migraines. Depakote use has been reported to be associated with teratogenic effects in the offspring of female patients receiving the drug during pregnancy. The risk was a concern to the sponsor to the degree that in the efficacy studies, women of childbearing potential were either excluded (Study 556) or included only if they did not become pregnant during the study and practiced effective birth control (study 881). For safety concerns, the use of this drug should be discouraged in female patients who intend on becoming pregnant or do not practice effective birth control. This information may be considered appropriate for this section under 201.57(c)(3)(ii)." [REF 6]

The FDA reviewer stated that VPA should be <u>discouraged</u> in female patients who intend on becoming pregnant or do not practice effective birth control. This was written in JUN 1994.

For their Study M00-232 (conducted by Abbott in 2000) on Comparison of Bioavailability of Depakote ER (1000 mg and 1500 mg total daily dose) Relative to Depakote DR (875 and 1250 mg total daily dose) in Healthy Volunteers, Abbott excluded "Female patients of childbearing potential unless total abstinence or reliable birth control method". [REF 9] More recent clinical trials require "female patients must be surgically sterilized or postmenopausal" (Univ. of MI 2013, REF 42]

Abbott did put the following statement in the Patient Information Leaflet (MAR 1996 through APR 2002/PDR 2004) for women taking VPA for migraines "Women taking Depakote for the prevention of migraine who are planning to get pregnant should discuss with their doctor temporarily stopping Depakote, before and during pregnancy." Immediately above this statement is a misrepresentation of the spina bifida data (see Sections 3.1 and 3.5 of this report). It is also unknown at this time how these Patient Information Leaflets were distributed.

The Abbott labeling (including Patient Information Leaflets) from marketing through 2012 do not state that patients must be practicing effective birth control before taking VPA as for the inclusion/exclusion criteria in the Abbott clinical studies.

3.5 Patient Information Leaflet

The following information is part of the Patient Information Leaflet distributed by Abbott relating to Depakote. *(JAN 1998/ PDR 1999 edition 53, Depakote).*

The leaflet is specifically for women who could become pregnant and taking Depakote for migraine – no other indications. Any women taking Depakote for an epilepsy indication would not read past the title of this leaflet because according to Abbott, it doesn't apply to them. Epileptic patients taking Depakote are left with the impression that spina bifida risk does not apply to them even though this risk clearly exists since Abbott cites the spina bifida risk from the Lyon France study done on women taking valproic acid for epileptic indications. But the leaflet is specifically "for migraine":

> "**Important Information for Women Who Could Become Pregnant About the Use of Depakote® (divalproex sodium) Tablets for Migraine**
>
> Please read this leaflet carefully before you take Depakote® (divalproex sodium) tablets. This leaflet provides a summary of important information about taking Depakote for migraine to women who could become pregnant. Depakote is also prescribed for uses other than those discussed in this leaflet.

If you have any questions or concerns, or want more information about Depakote, contact your doctor or pharmacist.

Information for Women Who Could Become Pregnant
Depakote is used to prevent or reduce the number of migraines you experience. Depakote can be obtained only by prescription from your doctor. The decision to use Depakote for the prevention of migraine is one that you and you doctor should make together, taking into account your individual needs and medical condition.

Before using Depakote, women who can become pregnant should consider the fact that **Depakote has been associated with birth defects, in particular, with spina bifida and other defects related to failure of the spinal canal to close normally. Although the incidence is unknown in migraine patients treated with Depakote, approximately 1 to 2% of children born to women with epilepsy taking Depakote in the first 12 weeks of pregnancy had these defects (based on data from the Centers of Disease Control, a U.S. agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%.**

…

Facts About Migraine
About 23 million Americans suffer from migraine headaches. About 75% of migraine sufferers are women. …

Abbott misrepresented the data from the Lyon France study to women who could become pregnant while taking Depakote. The following facts apply to the Lyon France study – from which the "1 to 2%" number is generated and reported on in the Abbott leaflet.

- The Lyon France study only gave data for spina bifida. It did not include any data on "other defects related to failure of the spinal canal to close normally." The "these defects" is incorrect.
- The "1 to 2%" is not an incidence number as implied by Abbott in its Patient Information Leaflet. It is a calculated estimated risk.
- The data is from a study in Lyon France and the CDC calculated the estimated risk from this Lyon France data and the incidence of spina bifida (0.06% - only spina bifida) in the general US population in 1983.
- The statement "The incidence in the general population is 0.1 to 0.2%" is presented as a comparator to the "1 to 2%" and they cannot be compared. One is only spina bifida, the other includes spina bifida and other neural tube defects. One is a calculated estimated risk and the other is an incidence.

- By mixing numbers between spina bifida data and spina bifida and neural tube defects data, Abbott presents information that shows about a 10 times greater risk for spina bifida for patients taking valproic acid than those not taking valproic acid when the actual estimated data shows about a 26 times greater risk.

Abbott performed no studies to determine the incidence of spina bifida or any other birth defects for pregnant women using Depakote; birth defect incidence is determined from prospective studies. Incidence cannot be determined from a retrospective study such as the Lyon France study; a calculated estimated risk was determined from the Lyon France data by the CDC.

Abbott's leaflet stated "… the incidence is unknown in migraine patients treated with Depakote …". But Abbott did have unintended pregnancies (8 pregnancies) in their migraine prophylaxis studies for Depakote ER/Depakote and did not report on the outcomes in this leaflet. *(see FDA Medical Review of Dr. Mark Ritter, 21 FEB 2008, page 43, NDA 22267, drugs@FDA).*

Abbott structured the Depakote Patient Information Leaflet only for women who could become pregnant for migraines and no other indications. Abbott did not give accurate information for "Women Who Could Become Pregnant" in their patient information leaflet. It was untrue and misleading and specific only to women taking Depakote for prophylaxis of migraines. Abbott was negligent.

3.6 North American Antiepileptic Drug Pregnancy Registry (NAAED Pregnancy Registry) [REF 21]

The NAAED Pregnancy Registry published the following article in March 2005: Increased rate of major malformations in offspring exposed to valproate during pregnancy *(Neurology, 64, 961-965)*. The article gave results of a prospective study of the rate of major malformations identified at birth in neonates whose mothers had taken VPA as monotherapy and were enrolled in the NAAED (1 FEB 1997 – 20 NOV 2003). The results showed the following:

> "Sixteen affected cases [with confirmed major malformations] were identified among 149 VPA-exposed women (proportion: 10.7%; 95% CI: 6.3 to 16.9%. The prevalence in the internal comparison group was 2.9% (95% CI: 2.0 to 4.1%; odds ratio: 4.0, 95% CI: 2.1 to 7.4; $p<0.001$). Assuming a 1.62% prevalence in the external comparison group, the relative risk of having an affected offspring for VPA-exposed women was 7.3% (95% CI: 4.4 to 12.2; $p<0.001$)".

The "internal comparison group" was women exposed to "all other AED monotherapies". The "external comparison group" was the number of cases (non-

genetic major malformations) expected on the basis of prevalence in the Active Malformations Surveillance Program at Brigham and Woman's Hospital.

Along with Elan, GlaxoSmithKline, Ortho-McNeil, Novartis and Pfizer, Abbott was one of the sponsors of the NAAED Pregnancy Registry. An abstract that published these results was published in 2004 entitled "Evidence of increased birth defects in the offspring of women exposed to valproate during pregnancy: findings from the AED Pregnancy Registry". *(Epilepsia, 45(11): 1465, 2004)* [REF 22].

The NAAED concluded "Women taking valproic acid were nearly three times more likely to have an infant with a birth defect than women taking another epilepsy drug. They were more than seven times more likely to have an infant with a birth defect than women in the general population." *(American Academy of Neurology, 21 MAR 2005).*

Of the 16 infants with major malformations, three had spina bifida. The major malformations included neural tube defects, craniofacial defects, cardiovascular malformations and malformation involving other body systems.

The FDA issued post-market safety information describing valproate and birth defect risk and the results of the NAAED Pregnancy Registry in a notice, entitled, "Information for Healthcare Professionals: Risk of Neural Tube Defects following prenatal exposure to Valproate" on 3 DEC 2009 [REF 26]. The notice stated "The FDA will be working with the manufacturers of these products to address the labeling changes." The FDA also recommended contraception in its statement "Women of childbearing potential should only use valproate if it is essential to manage their medical condition. Those who are not actively planning a pregnancy should use effective contraception, as birth defect risks are particularly high during the first trimester, before many women know they are pregnant." The women in the NAAED study who had children with spina bifida or other malformations had all taken the recommended dose of folic acid [REF 39]. The FDA also recommended pregnant women taking VPA or other AEDs enroll in the NAAED Pregnancy Registry.

Abbott added safety information to the Depakote (VPA) labeling about the results of major malformations caused by VPA from the NAAED Pregnancy Registry in its OCT 2006 (2008 PDR) labeling; this was years after Abbott first learned of the results from the NAAED Registry. Abbott is responsible for adding important safety information to its labeling and informing healthcare professionals as soon as possible.

3.7 Neurodevelopment Effects of Antiepileptic Drug (NEAD) Study – 2006 [REF 40 & 35]

In AUG 2006, Meador et al published a study (NAED Study), entitled, "In Utero antiepileptic drug exposure: fetal death and malformations", Neurology, AUG 8:

67(3); 407-412. The NAAED Study was an ongoing prospective observational study across 25 epilepsy centers in the US and UK (OCT 1999 – FEB 2004) and enrolled mother-child pairs. The four most commonly used AEDs were studied: carbamazepine, lamotrigine, phenytoin and valproate. Children were followed to age 6 to determine the cognitive and behavioral effects of in utero AED exposure. Since the study collected all in formation on adverse events occurring in the mother and child, in AUG 2006, the NAED study published the results of the incidences of serious adverse outcomes including major congenital malformations (which could be attributable to AEDs) or fetal death. The results showed a statistically significant higher risk of major birth defects for valproate compared to the other AEDs. The authors wrote "The current study by itself is not definitive, but compared with several other recent studies, it contributes to a considerable body of evidence that VPA poses a special risk to the unborn child." The serious adverse outcomes were: carbamazepine (9/110, 8.2%), lamotrigine (1/98, 1.0%), phenytoin (6/56, 10.7%), VPA (14/69, 20.3%). The prevalence of major birth defects by AED in the first 333 mother child pairs were: carbamazepine (5/110, 4.5%), lamotrigine (1/98, 1.0%), phenytoin (4/56, 7.1%), VPA (12/69, 17.4%) *(Lamotrigine Pregnancy Registry Report, Final Report, Glaxo, JUL 2010,* REF 35*).* The authors Meador et al concluded that "These results combined with several recent studies provide strong evidence that valproate poses the highest risk to the fetus".

3.8 VPA and Impaired Cognitive Development [REF 41 & 25]

When the American Academy of Neurology released its statement on 21 MAR 2005 about the results from the NAAED Pregnancy Registry about VPA and birth defects, it also included a summary of another study of children born to mothers who took VPA and the children's IQ scores *(American Academy of Neurology, New Studies Show Mixed Results on Epilepsy Drugs and Birth Defects, REF 25).* This study appeared in the same issue of the journal Neurology as the NAAED Pregnancy Registry publication in 2005 (http://www.medscape.com/viewarticle/501684#vp_2).

> "For the second study on valproic acid, British researchers recruited 163 mothers with epilepsy and their children and gave them a number of tests. A total of 249 children between the ages of 6 and 16 took the tests. The 41 children who were exposed to valproic acid during the pregnancy were more likely to have low verbal IQ scores (average of 84) compared to other groups in the study, such as those exposed to the drug phenytoin (average score of 99) or those not exposed to any epilepsy drug during pregnancy (average score of 92).
>
> Those exposed to valproic acid were also more likely to have overall IQ scores in the extremely low, or mentally impaired range. Two to three percent of the population would be expected to fall in this range. In the study, 22 percent of those exposed to valproic acid were in this range."

NAED Studies – 2009 & 2013 [REF 32 & 31]

The NAED Study Group published 2 reports (APR 2009 interim analysis & MAR 2013) relating to cognitive function in children whose mothers took antiepileptic drugs (carbamazepine, lamotrigine, phenytoin, valproate). The primary outcome was cognitive performance of the children at 6 years of age. The 2009 publication by NAED was the results of the planned interim analysis conducted when the children were 3 years of age. This interim analysis showed that "the maternal use of valproate during pregnancy is associated with an increased risk of cognitive impairment in children at 3 years of age. This information is relevant to counseling women of reproductive age regarding this drug class."

The NAED Study Group published the article entitled, "Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study." The results showed that "Fetal valproate exposure has dose-dependent associations with reduced cognitive abilities across a range of domains at 6 years of age."

FDA Communications [REF 28 & 27]

The FDA informed the public on 30 JUN 2011 with its communication "FDA Drug Safety Communication: Children born to mothers who took Valproate products while pregnant may have impaired cognitive development." This FDA communication addressed the results from the NAED interim study published in APR 2009.

….

The FDA advised healthcare professionals and women on 6 MAY 2013 with its communication "FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children". The FDA advised that VPA is contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. This contraindication for VPA was based on the MAR 2013 NAED publication that showed evidence that VPA can cause decreased IQ scores in children whose mothers took VPA while pregnant. The FDA stated "All non-pregnant women of childbearing age taking valproate should use effective birth control." The women in the NAED study were exposed to antiepileptic drugs throughout their pregnancies.

Abbott knew from at least MAR 2005 (from published literature - American Academy of Neurology) that VPA can cause decreased IQ scores in children whose mothers took VPA while pregnant and those exposed to VPA were more likely to have IQ scores that were extremely low or showed mentally impairment. It was not

until Abbott's VPA labeling of 7 OCT 2011 that safety information about decreased IQ scores was put in the labeling. Abbott is responsible for its labeling.

3.9 Abbott's Lack of a Pregnancy Exposure Registry for Depakote

On September 21, 1989, the FDA Division of Drug Advertising and Labeling sent Abbott a letter regarding an industry complaint about advertising materials disseminated by Abbott for unapproved indications for Depakote *(FDA/Abbott Correspondence of 1989, FOI Services #85531A).* Abbott responded to the FDA on October 25, 1989 and as part of that response, Abbott addressed a literature article relating to breakthrough bleeding of women on concomitant oral contraceptives and the comparison of this breakthrough bleeding of various anticonvulsants and valproate sodium. In Abbott's response, they stated the following:

> "Spontaneous reports to a drug manufacturer are not an accurate indicator of the incidence of a side effect, when compared with a prospective or retrospective study of a patient population."

I agree with that statement by Abbott. For pregnant patients taking a known teratogen such as VPA (Depakote), spontaneous reports to Abbott will not give the incidence of a birth defect or congenital abnormalities since spontaneous reports are retrospective. However, Abbott did know that "malformations" was the most commonly reported adverse event (6% of adverse events) from 1977 – 1997 for sodium valproate to the ADRAC - Australian Drugs Reaction Committee *(http://www.sanofi.com.au/products/aus_pi_epilim.pdf).*

Prospective reports are the way to determine an incidence of a birth defect or congenital abnormality or the incidence of major birth defects. Prospective reports for pregnant patients are done through a Pregnancy Exposure Registry for a marketed product. Abbott never started or set-up any Pregnancy Exposure Registry for VPA when it began its marketing of Depakene or Depakote even though VPA was a known human teratogen. Abbott never had any intention of determining the incidence of major birth defects or identifying other birth defects caused by VPA in any prospective study.

The Black Box Warning for the labeling for Depakote has the following "VALPROATE CAN PRODUCE TERATOGENIC EFFECTS SUCH AS NEURAL TUBE DEFECTS (E.G., SPINA BIFIDA), ACCORDINGLY, THE USE OF DEPAKOTE TABLETS IN WOMEN OF CHILDBEARING POTENTIAL REQUIRES THAT THE BENEFITS OF ITS USE BE WEIGHED AGAINST THE RISK OF INJURY TO THE FETUS. …" Abbott's labeling requires that physicians and healthcare professionals weigh the benefits of its use against the risk of injury to the fetus. For healthcare professionals/physicians to accomplish this required benefit/risk assessment, it is Abbott's responsibility to identify the risks to the best of its ability in the labeling. Abbott did not do this

throughout its labeling – literature reports with safety data on birth defects were not added, a pregnancy exposure registry was not initiated, clinical trial pregnancy outcome data from unintended pregnancies were not reported and there was no safety information on the neonates, infants and children whose mother's were taking VPA during pregnancy. Abbott failed to adequately provide physicians/healthcare professionals and patients with important and necessary information about the "risk of injury to the fetus" to make their required benefit/risk assessment. Abbott was required as part of its post-marketing safety surveillance program for VPA to provide that necessary risk information in the labeling so that physicians/healthcare professionals could make their required benefit/risk assessments.

Pregnancy Exposure Registries – Industry Standard in Post-Marketing Surveillance

Pharmaceutical companies were using pregnancy exposure registries as a way to collect outcome data on the fetuses, neonates, infants and children of pregnant patients taking pharmaceutical drugs during the timeframe of the marketing of Depakene and Depakote. This was especially true for new chemical entities and drugs that were being given to women of childbearing age. A few examples of the pregnancy exposure registries sponsored by pharmaceutical companies as part of their postmarketing surveillance include:

- Lamotrigine Pregnancy Registry, sponsored by GlaxoSmithKline (*http://pregnancyregistry.gsk.com/documents/lam_spring_2010_final_report.pdf*)

  "Lamotrigine is a second generation anticonvulsant therapy. The medical division of GlaxoSmithKline established this Registry as part of an ongoing program in postmarketing surveillance epidemiologic surveillance because of the potential for exposure in the first trimester of pregnancy, the potential risks for any new chemical entity the known teratogenicity of specific existing anticonvulsants, and the suspected increased risk of teratogenicity with polytherapy. … Registry data are provided to supplement animal toxicology studies and to assist clinicians in weighing the potential risks and benefits of treatment for individual patients."

  The Lamotrigine Pregnancy Registry covered the period 1 SEP 1992 through 21 MAR 2010.

  The Lamotrigine Pregnancy Registry analyzed its data on pregnancy outcomes using three exposure groups: Lamotrigine Monotherapy, Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate and Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate. The data were further analyzed according to trimester lamotrigine exposures.

The report had the following summary for "Polytherapy including Valproate":

> "In the prospective reports with first trimester exposure to polytherapy including valproate, there were 16 major birth defects reported in 150 outcomes. … The observed proportion of births with major defects was 10.7% (95% Confidence Interval: 6.4% - 17.0%) (Fleiss 1981). This exposure group exhibited the highest proportion with major defects following first trimester exposures."

As a comparison, for the first trimester exposure, the observed proportion of births with major defects was 2.2% (95% Confidence Interval: 1.6% - 3.1%) for lamotrigine monotherapy and 2.8% (95% Confidence Interval: 1.5% - 5.0%) for polytherapy not including valproate.

- Bupropion Pregnancy Registry, sponsored by GlaxoSmithKline (*http://pregnancyregistry.gsk.com/documents/bup_report_final_2008.pdf*)

  "Bupropion is available by prescription for the treatment of depression … and for smoking cessation. … The medical division of GlaxoSmithKline established a program in postmarketing epidemiologic surveillance because of the potential exposure in the first trimester and the potential risks for any new chemical entity. … Registry data are provided to supplement animal toxicology studies and to assist clinicians in weighing the potential risks and benefits of treatment for individual patients."

  The Bupropion Pregnancy Registry covered the period 1 SEP 1997 through 31 MAR 2008.

Abbott failed to establish a Pregnancy Exposure Registry for pregnant women taking VPA as part of their postmarketing surveillance program. Abbott failed to provide Pregnancy Registry Exposure participation information for the NAAED Pregnancy Registry (that it partially financed) for patients taking VPA for epilepsy in its labeling and failed to establish its own Pregnancy Exposure Registry for the indications of mania/bipolar and prophylaxis of migraines as part of its postmarketing surveillance.

3.10 Literature Reports

There are numerous publications that summarize the published literature regarding VPA and birth defects/malformations. Two of these publications are summarized below.

KJ Meador, et al, In Utero antiepileptic drug exposure: fetal death and malformations, Neurology, 2006 AUG 8: 67(3); 407-412 (NAED Study) [REF 40]

References to high/higher rates of birth defects/malformations for VPA include:

NAAED Pregnancy Registry (2005)
Australian Pregnancy Registry (2005)
International Lamotrigine Pregnancy Registry (2005)
Swedish Medical Birth Registry (2004)
Finnish National Medical Birth Registry (2005)
United Kingdom Pregnancy Registry (2005)
8 other references (1999 through 2005)

The literature was summarized with the following "In summary, the addition of the current NAED Study findings brings the total to 14 different cohorts (10 significant) in which children exposed to VPA have had worse outcomes than children exposed to other AEDs or nonexposed children."

D.F.Wyszynski, L.B. Holmes, et al, Increased rate of major malformations in offspring exposed to valproate during pregnancy, Neurology 64, Mar 2005, 961-965 (NAAED Pregnancy Registry) [REF 21]

The literature was summarized:

"A common major malformation attributed to exposure to VPA was neural tube defects (NTDs)" - cited 8 references (1982 -1992)
"The risk of an NTD may be as high as 5% at high VPA exposures." – cited one reference (1982)
"Other congenital malformations associated with this exposure have included heart defects, oral clefts, genital abnormalities, and limb defects." – cited 8 references (1988 – 2003)

There were literature reports that showed that the risk of neural tube defects may be as high as 5% at high VPA exposures (1982 -1992). Abbott never put this information in its labeling of VPA.

There were reports in the literature from at least 10 significant cohorts [REF 40] which showed that children exposed to VPA had worse outcomes than children exposed to other AEDs or non-exposed children (1999-2005). Abbott never put this literature information in its labeling through those years.

3.11 FDA Regulations

21 CFR 314.80(b) Postmarketing reporting of adverse drug experiences (current regulation, 2017)

> (b) *Review of adverse drug experiences.* Each applicant having an approved application under 314 .50 or, in the case of a 505(b)(2) application, an effective approved application, must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all followup information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section must also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

The regulation to "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA" was published on 7 OCT 1997 and made effective by the FDA on 6 APR 1998. Also, according to the FDA, it was "usual and customary" to have such written procedures in place by applicants and manufacturers before 7 OCT 1997. Abbott is required to have SOPs in place for the surveillance, receipt and evaluation (and reporting) of all adverse drug experience information to the FDA. All important risk information must be put in the labeling from post-marketing activities.

FDA regulations permit a manufacturer to make certain changes to its label before receiving the agency's approval. Among other things, this "changes being effected" (CBE) regulation provides that if the manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution or adverse reaction" or to "add or strengthen an instruction about dosage and administration this is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval. [21 CFR 314.70(c)(6)(iii)(A)].

It has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. See, e.g., 21 CFR 201.80(e) (requiring a manufacturer to revise its label "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"); 314.80(b) (placing responsibility for postmarketing surveillance on the manufacturer; 73 Fed. Reg. 49605 ("Manufacturers continue to have responsibility under Federal law … to maintain their labeling and update the labeling with new safety information"). *(see Supreme Court Wyeth v Levine, decided 4 MAR 2009).*

3.12 Clinical Studies Data on Unintended Pregnancies

There were many unintended pregnancies during the clinical trials that Abbott conducted under their IND for various indications for VPA.

Depakote Tablets: Mania/Bipolar Disorder, NDA 20-320, MAY 1995

The FDA Clinical Review (Earl Hearst, MD) of the double-blind, placebo-controlled studies (M87-016, M88-267) and open-label studies (M90-552, M91-706) that Abbott conducted for its indication of treatment of mania/bipolar disorder showed the following unintended pregnancies *(FDA Clinical Review, 05/26/1995, FOI Services 522047)*:

> "**8.5.7 Human Reproduction Data**
> There were 5 pregnancy-related events in four patients. Three pregnancies ended in abortion, (1-elective, 1-miscarriage, 1-unknown). In one unintended pregnancy the outcome is unknown and in the final case there was a placental disorder and fetal disorder with delivery by C-section of a 2345 gm infant with apgar of 6 at one minute and 8 at 5 minutes. Depakote is known to be teratogenic."

Two of the abortions were identified as Patient M90-552/2016 and Patient M90-552/2101 and were considered "unlikely to be drug related". There was one death attributed to a congenital anomaly reported from post-marketing spontaneous reports from September 1, 1992 through February 1, 1995; this AE was reported under the review of deaths and the review does not list non-death congenital abnormalities.

Additional information from Case Report Forms (CRFs) is not known at this time. Also, it is not known at this time the inclusion/exclusion criteria for all the clinical studies conducted. The FDA did clearly state "Depakote is known to be teratogenic."

Depakote ER Tablets: Mania/Bipolar & Prophylaxis of Migraines, NDA 22-267, SEP 2007

The FDA Medical Review (Mark Ritter, MD) states that there were 8 pregnancies under the migraine prophylaxis studies. It is not clear at this time if this is a reference to the Depakote DR (delayed release) or Depakote ER (extended release) migraine prophylaxis studies.

Summary

I do not have much information on the outcomes of the unintended pregnancies from Abbott's development of VPA in the clinical studies – at this time. This

information has been requested and, as it becomes available, it will be compiled. It is noted that in the NAAED Pregnancy Registry, 16 cases of congenital abnormalities were found in 149 VPA-exposed women. Since pregnant patients in the clinical trials are a source of prospective patients, it is important that follow-ups for pregnancy outcome information be obtained and appropriately analyzed; there is no indication, at this time, that this was done by Abbott.

3.13 US Department of Justice: Abbott Criminal and Civil Investigation [REF 36 & 37]

On 7 MAY 2012, the Department of Justice (DOJ) announced that Abbott "pleaded guilty and agreed to pay $1.5 billion to resolve its criminal and civil liability arising from the company's unlawful promotion of the prescription drug Depakote for uses not approved as safe and effective by the Food and Drug Administration (FDA). … Abbott has pleaded guilty to misbranding Depakote by promoting the drug to control agitation and aggression in elderly dementia patients and to treat schizophrenia when neither of these uses was FDA approved. … The company admits that from 1998 through 2006, the company maintained a specialized sales force trained to market Depakote in nursing homes for the control of agitation and aggression in elderly dementia patients, despite the absence of credible scientific evidence that Depakote was safe and effective for that use. In addition, from 2001 through 2006, the company marketed Depakote in combination with atypical antipsychotic drugs to treat schizophrenia …"

Acting Associate Attorney General Tony West stated "Not only did Abbott engage in off-label promotion, but it targeted elderly dementia patients and downplayed the risks apparent from its own clinical studies. As this criminal and civil resolution demonstrates, those who put profits ahead of patients will pay a hefty price."

Just as the DOJ concluded that Abbott downplayed the risks of Depakote apparent from its own clinical studies in the Depakote criminal and civil investigations and off-label promotion for elderly dementia patients, Abbott also downplayed the risks of Depakote with regard to birth defects in its labeling apparent to published literature studies, its own clinical studies (no mention of prospective outcomes from unintended pregnancies) and provided no statement requiring effective birth control for women of childbearing age (as it did in its clinical studies).

Abbott promoted Depakote for off-label indications, putting patients at risk by giving healthcare providers and the public inaccurate efficacy and safety information.

4. ADDITIONAL INFORMATION REQUESTED

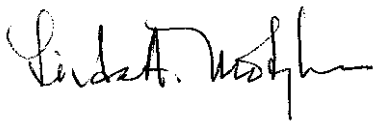
- All correspondence between Abbott and Glaxo regarding the Lamotrigine Pregnancy Registry results for VPA
- All correspondence between Abbott and L.B. Holmes (and/or the NAAED Pregnancy Registry)
- All correspondence between Abbott and FDA on Depakote and birth defects
- All correspondence between Abbott and any/all of the following: Australian Pregnancy Registry, Swedish Medical Birth Registry, Finnish National Medical Birth Registry, United Kingdom Pregnancy Registry.
- All correspondence between Abbott and Sanofi on VPA and birth defects.
- Depakote NDA submissions of ISS (Integrated Summaries of Safety)
- All Investigator Brochures for Depakote (1983 – present)
- All Abbott safety reports on Depakote and birth defects
- All Abbott literature summaries on Depakote and birth defects
- Final Study Reports (including all appendices) for: M91-556, M92-811, M91-647, M98-845, M98-924, M87-016, M88-267, M90-552. Case Report Forms for M90-552 (Patients 2061 and 2101).
- All Standard Operating Procedures (SOPs) that comply with 21 CFR 314.80(b) and all SOPs for Clinical Studies and Pregnancy (1980 – present, all versions)

5. CONCLUSIONS

- Abbott did not put the following statement in the Warnings Section of their labeling of Depakote/Depakene/Depacon from years 1983 – 2012 as required by FDA regulation 21 CFR 201.57(f)(6). "Depakote (*name of drug)* can cause fetal harm when administered to a pregnant woman."
- Abbott failed to adequately provide physicians/healthcare professionals and patients with important and necessary information about the "risk of injury to the fetus" to make their <u>required</u> benefit/risk assessment.
- Abbott failed to establish a Pregnancy Exposure Registry for pregnant women taking VPA as part of their postmarketing surveillance program. Abbott failed to provide Pregnancy Registry Exposure participation information for the NAAED Pregnancy Registry for patients taking VPA for epilepsy in its labeling and failed to establish its own Pregnancy Exposure Registry for the indications, including mania/bipolar and prophylaxis of migraines as part of its postmarketing surveillance.
- Since pregnant patients in the clinical trials are a source of prospective patients, it is important that follow-ups for pregnancy outcome information be obtained and appropriately analyzed; there is no indication, at this time, that this was done by Abbott.
- Just as the DOJ concluded that Abbott downplayed the risks of Depakote apparent from its own clinical studies in the Depakote criminal and civil

investigations and off-label promotion for elderly dementia patients, Abbott also downplayed the risks of Depakote with regard to birth defects in its labeling apparent to published literature studies, its own clinical studies (no mention of prospective outcomes from unintended pregnancies) and provided no statement requiring effective birth control for women of childbearing age (as it did in its clinical studies).

- Abbott misrepresented in its labeling the estimated risk of spina bifida from the Lyon France study data for about 35 years.
- There were literature reports that showed that the risk of neural tube defects may be as high as 5% at high VPA exposures (1982 -1992). Abbott never put this information in its labeling of VPA.
- There were reports in the literature from at least 10 significant cohorts [REF 40] which showed that children exposed to VPA had worse outcomes than children exposed to other AEDs or non-exposed children (1999-2005). Abbott never put this literature information in its labeling through those years.
- Abbott knew from at least MAR 2005 (from published literature - American Academy of Neurology) that VPA can cause decreased IQ scores in children whose mothers took VPA while pregnant and those exposed to VPA were more likely to have IQ scores that were extremely low or showed mentally impairment. It was not until Abbott's VPA labeling of 7 OCT 2011 that safety information about decreased IQ scores was put in the labeling. Abbott is responsible for its labeling.
- Abbott added safety information to the Depakote (VPA) labeling about the results of major malformations caused by VPA from the NAAED Pregnancy Registry in its OCT 2006 (2008 PDR) labeling; this was years after Abbott first learned of the results from the NAAED Registry. Abbott is responsible for adding important safety information to its labeling and informing healthcare professionals as soon as possible.
- Abbott promoted Depakote for off-label indications, putting patients at risk by giving healthcare providers and the public inaccurate efficacy and safety information.
- Abbott did not review clinical literature in an effort to update its labeling for VPA.
- Abbott did not discourage female patients from using VPA in its labeling who intended to become pregnant or who were not practicing effective birth control.



Linda A. Motyka, Ph.D. September 26, 2017